UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/333,110	06/15/1999	DON STRAUS	50050/002001	3733

7590 02/21/2002

PAUL T CLARK
CLARK & ELBING LLP
176 FEDERAL STREET
BOSTON, MA 02110

EXAMINER	
EINSMANN, JULIET CAROLINE	
ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 02/21/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/333,110	STRAUS, DON	
	Examiner	Art Unit	
	Juliet C Einsmann	1655	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 November 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-60* is/are pending in the application.

4a) Of the above claim(s) *21-46 and 55-57* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-20,47-54 and 58-60* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Continued Prosecution Application

1. The request filed on 11/20/01 for a Continued Prosecution Application (CPA) under 37 CFR 1.53(d) based on parent Application No. 09/333110 is acceptable and a CPA has been established. An action on the CPA follows.

2. No amendments or arguments were filed with the request for CPA. Claims 1-60 are pending. Claims 21-46 and 55-57 are withdrawn from consideration as being drawn to a non-elected invention. Claims 1-20, 47-54, and 58-60 are examined herein.

3. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Specification- Sequence Rules

4. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821-1.825 because there is no sequence listing and no CRF has been submitted. See, for example, pages 73 and 78. Applicant is required to submit a CRF and paper copy of the Sequence Listing containing these sequences, an amendment directing the entry of the Sequence Listing into the specification, an amendment directing the insertion of the SEQ ID NOs into the appropriate pages of the specification and a letter stating that the content of the paper and computer readable copies are the same.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 59-60 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. MPEP 2163.06 notes "If new matter is added to the claims, the examiner should reject the claims under 35 U.S.C. 112, first paragraph - written description requirement. In re Rasmussen , 650 F.2d 1212, 211 USPQ 323 (CCPA 1981)."

In the instantly rejected claims, the new limitation of "without purifying said nucleic acid molecules from said sample" in claims 59 and 60 appears to represent new matter. No specific basis for this limitation was identified in the specification, nor did a review of the specification by the examiner find any basis for the limitation. Specifically, the exclusion proviso in which "without purifying" is required is not found in the specification. As noted by MPEP 2173.05(i),

> "Any negative limitation or exclusionary proviso must have basis in the original disclosure. See Ex parte Grasselli , 231 USPQ 393 (Bd. App. 1983) aff'd mem., 738 F.2d 453 (Fed. Cir. 1984). The mere absence of a positive recitation is not basis for an exclusion. Any claim containing a negative limitation which does not have basis in the original disclosure should be rejected under 35 U.S.C. 112, first paragraph as failing to comply with the written description requirement."

Since no basis has been identified, the claims are rejected as incorporating new matter.

Claim Rejections - 35 USC § 112

6. Claims 5-7, 16-19, 47, and 52-54 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 5 and 6 are indefinite because it is unclear how the amplified probes are used in the method of the base claim. Step b) of the base claim indicates that it is a hybridization step of the nucleic acid molecules of step (a) with the detection ensemble. If the amplified probes are intended to be the amplification products of step (a)(iii) then the claim should be amended to clarify this point.

Claim 7 is indefinite over the amendment which indicates that the *in situ* hybridization should occur "following step (b)." In step (b) the target nucleic acid molecules are detected, and so it is unclear what exactly is being hybridized in the *in situ* hybridization step. The current claim directs that the detection of the target nucleic acid occurs, and after that a quantification by *in situ* hybridization occurs. If it is Applicant's intent that the detection step of (b) occur *in situ*, this is not clear.

Claims 16-19 are indefinite over the recitation "wherein said target nucleic acids in said sample comprise" because it is not clear if the claim is meant to require that the sample itself contain nucleic acids from 6 or more of the listed organisms OR if the detection ensemble should be able to detect 6 or more of the listed organisms. That is, the claim appears to be requiring that 6 or more of the listed organisms be present in the sample, yet this is confusing, because the

claim is also directed to detecting the presence of target nucleic acid molecules. Clarification is required.

Claims 16-19 are indefinite over the recitation of "comprise 6 or more different nucleic acid molecules from" because it is not clear if the intention of the claim is that there be 6 or more different nucleic acid molecules from different parts of each of the organisms recited OR if there should be nucleic acids which represent 6 or more of the different organisms recited. It appears that improper Markush language is being used in these claims.

Claim 47 is indefinite because it is not complete. The amended claim ends with step (b), and does not end with a period.

Claims 52-54 are indefinite for the recitation of "the amplification products of step (a)(iv)" because step (a)(iv) refers to genomic representations, while step (a)(iii) refers to amplification products.

Claim Rejections - 35 USC § 102

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

8. Claims 1, 2, 3, 4, 5, 6, 8, 9, 10, 11, 12, 14, 18, 20, 47, 52, 54, and 58 are rejected under 35 U.S.C. 102(b) as being anticipated by Greisen *et al.* (Journal of Clinical Microbiology, Feb 1994, p. 335-351).

Greisen *et al.* teach a method for detecting target nucleic acid molecules in a biological sample potentially comprising such target nucleic acid molecules, said method comprising the steps of:

(a) providing nucleic acid molecules that are (ii) probes that hybridize to the target nucleic acid molecules in said sample (p. 336); and

(b) detecting target nucleic acid molecules by contacting or comparing the nucleic acid molecules of (a) with a detection ensemble of nucleic acid sequences that has a minimum genomic derivation of greater than five and that comprises nucleic acid detection sequences that can detect the nucleic acid molecules of (a) (p. 338, Table 3).

Greisen *et al.* further teach (c) identifying nucleic acid molecules detected in step (b) (p. 349, last paragraph) (Claim 2).

The genomic derivation of the detection ensemble used by Greisen *et al.* is greater than 11 (Table 3) (Claim 3).

Greisen *et al.* teach a step prior to step (a) in which nucleic acid molecules of said sample are hybridized with an ensemble of ID probes (universal primers) and extended in an amplification reaction to yield the probes of step (a)(ii) (p. 336 and p. 340) (Claims 8, 5, and 6) (p. 340). The probes of (a)(ii) thus have a first region capable of hybridizing to a target nucleic acid molecule and an amplification sequence (Claim 9). The probes of a(ii) are fixed to a solid

support (p. 336) (Claim 10). The probes of step (a) used by Greisen *et al.* all inherently comprise one or more oligonucleotide tags as they all have primer sequences incorporated into the nucleic acids (Claim 12).

Greisen *et al.* further teach a method in which the probes of the instant invention are immobilized on a solid support, such as a reverse dot blot format or a microwell plate format (p. 350). In such a method, the detection sequences are arrayed as spots in two dimensions and the nucleic acid molecules of step (a) are not immobilized in a matrix, but are in solution (claims 4, 11 and 14). Furthermore, in such a method the hybridization of the probes with the detection ensemble is simultaneous (claim 47).

Greisen *et al.* teach that samples that can be examined using their methodology include blood (p. 335), and the detection ensemble taught by Greisen *et al.* comprises probes specific to *Bacteriodes*, *Streptococcus pneumoniae, E. coli, Corynebacterium*, coagulase negative *Staphylococcus*, and *Staphylococcus aureus,* thus comprising 6 or more of the organisms listed in claim 18 (Table 3).

The detection ensemble taught by Greisen *et al.* is comprised entirely of probes that are capable of hybridizing to pre-determined genomic difference sequences that are potentially present in said sample (Table 4 and p. 342) (Claim 20).

Claim 52 is anticipated, because the amplification products provided by Greisen *et al.* are made using two primers (p. 340).

Claim 54 is anticipated because the detection ensemble comprises ID sites that are congruent to ID probes potentially amplified in step (a)(iii).

9. Claims 1-4, 8-14, 20, and 47-52 are rejected under 35 U.S.C. 102(e) as being anticipated by Shuber (US PAT 5834181).

Shuber teaches methods for obtaining genetic information from a biological sample comprising (a) providing a sample containing target nucleic acid molecules and (b) detecting the target molecules by contacting the sample with hybridization probes and identifying the hybridized probes (abstract). Shuber specifically teaches that the method can be used with 10-200 probes, preferably allele specific oligonucleotides (Col. 7, lines 11-14). Shuber teaches multiple embodiments for his invention.

With respect to claims 4 and 11, Shuber teaches that it may be desirable to hybridize the polymers to the target in solution, i.e. without having bound the target to a support (Col. 6, line 66-Col. 7, line 4).

With respect to claims 8 and 14, Shuber further teaches that hybridized probes can be identified by the use of hybridization arrays, wherein members of the probe pool are separated from the target nucleic acids and re-hybridized to immobilized probes on an array (Col. 9, line 65-Col. 10, line 10). In this case, the method of Shuber comprises obtaining genetic information from a sample by (a) providing probes that hybridized to target nucleic acid molecules in a sample and (b) detecting the probes using an ensemble of probes, wherein the detection ensemble is immobilized on an array, wherein the probes of step (a) were obtained by first hybridizing a probe pool (ensemble of ID probes) with the sample and then separating them from the sample.

With respect to claim 10, Shuber teaches an embodiment in which the target nucleic acid is bound to a solid phase matrix (Col. 6, line 42-43).

With respect to claim 12, Shuber teaches that oligonucleotide probes can be synthesized to contain sequences complementary to the target region and additional pre-determined sequences that act as "tags" (Col. 10, lines 25-27).

With respect to claims 9 and 13 and 52, Shuber discloses in example 9 embodiment of the invention in which ligation based techniques are used (Col. 25, heading Example 9). In this case, probes that are intended to hybridize with the target are ligation probes and the ligation probes flank the site of a genetic alteration (Col. 26, lines 14-16). Shuber teaches that some probes which identify genetic alteration include ASO probes, which target small changes relative to the prevalent "wild type" sequence, including a single nucleotide (as in single nucleotide polymorphisms (SNP)) (Col. 4, lines 40-48). Shuber teaches that after ligation the ligated products can be amplified using LCR or PCR (Col. 26, lines 31-34), specifically teaching that one method for identification of ligated probes is to use the ligation product as a template for a linear amplification using a universal priming sequence (Col. 26, lines 63-66).

With respect to claims 50-51 in which greater than 20 or 50 probes must be used, note, as mentioned above, that Shuber teaches the methods of this invention can be used with 10-200 probes, preferably allele specific oligonucleotides (Col. 7, lines 11-14).

10. Claims 1-4, 9, 11-15, 19-20, 47-48 and 52 are rejected under 35 U.S.C. 102(b) as being anticipated by Barany et al. (WO 97/31256).

Barany et al. teach a method for identifying a plurality of sequences differing by one or more single base changes, insertions, deletions or translocations in a plurality of target nucleotide sequences (abstract). The method comprises (a) providing a sample containing target nucleic acid molecules (p. 6, lines 13-15) (b) detecting the target nucleic acid molecules by means of a hybridization phase in which two probes suitable for ligation when hybridized adjacent to one another on a target nucleic acid are hybridized to a target molecule and ligated (p. 6, lines 25-30) and (c) identifying the nucleic acid molecule by means of a capture phase in which the probes are captured on an addressable array (p. 6, lines 35-40) and identity is determined based on their position on the array (p. 7, lines 3-7).

The method is exemplified in figure 8 wherein a single pair of amplification primers is used to amplify the region containing a mutation, and then a probe sets are used to detect different mutations in two different codons. In this example there are twenty possible mutation combinations. Barany et al. teach that the probe ligation reactions are solution based (p. 48, lines 30-31), and one of each set of probes to be ligated comprises an oligonucleotide tag that will be useful for capture on the addressable array (p. 6, line 30). Barany et al. teach that this method is useful to determine the presence of viruses in a sample, including HIV, human T-cell lymphocytotrophic virus, hepatitis viruses, Epstein-Barr Virus, cytomegalovirus, human papillomaviruses, orthomyxo viruses, paramyxo viruses, adenoviruses, corona viruses, bunya viruses, and toga viruses (p. 21, lines 11-16).

Claim Rejections - 35 USC § 103

11. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

12. Claim 13 is rejected under 35 U.S.C. 103(a) as being unpatentable over Greisen *et al.* in view of Barany *et al.*

Greisen *et al.* teach a method for detecting target nucleic acid molecules in a biological sample potentially comprising such target nucleic acid molecules, said method comprising the steps of:

(a) providing nucleic acid molecules that are (ii) probes that hybridize to the target nucleic acid molecules in said sample (p. 336); and

(b) detecting target nucleic acid molecules by contacting or comparing the nucleic acid molecules of (a) with a detection ensemble of nucleic acid sequences that has a minimum genomic derivation of greater than five and that comprises nucleic acid detection sequences that can detect the nucleic acid molecules of (a) (p. 338, Table 3).

Greisen *et al.* do not provide a method in which at least some of the probes of step (a)(ii) comprise two or more oligonucleotides that can be ligated to one another upon hybridization to a target nucleic acid molecule, and (ii) amplification sequences (claim 13).

Barany et al. teach a method for identifying a plurality of sequences differing by one or more single base changes, insertions, deletions or translocations in a plurality of target nucleotide

sequences (abstract). The method comprises (a) providing a sample containing target nucleic acid molecules (p. 6, lines 13-15) (b) detecting the target nucleic acid molecules by means of a hybridization phase in which two probes suitable for ligation when hybridized adjacent to one another on a target nucleic acid are hybridized to a target molecule and ligated (p. 6, lines 25-30) and (c) identifying the nucleic acid molecule by means of a capture phase in which the probes are captured on an addressable array (p. 6, lines 35-40) and identity is determined based on their position on the array (p. 7, lines 3-7).

Barany et al. teach that the probe ligation reactions are solution based, thus, the nucleic acid molecules are not immobilized in a matrix or on a solid support (p. 48, lines 30-31), and one of each set of probes to be ligated comprises an oligonucleotide tag that will be useful for capture on the addressable array (p. 6, line 30). Barany et al. teach that this method is useful to determine the presence of a wide range of infectious disease causing agents, including many bacterial pathogens (p. 20-21).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have modified the methodology provided by Greisen *et al.* to use methodology taught by Barany *et al.* with a detection ensemble specific for the different pathogens as taught by Greisen *et al.* The ordinary practitioner would have been motivated to make the necessary modifications to the methods taught by Greisen *et al.* because Barany *et al.* teach the benefits of their methodology, including "its ability to carry out multiplex analyses of complex genetic systems. As a result, a large number of nucleotide sequence differences in a sample can be detected at one time (p. 7, lines 26-29)."

13. Claims 5, 6, and 58 are rejected under 35 U.S.C. 103(a) as being unpatentable over Shuber in view of Straus *et al.* (PNAS USA Vol. 87, pp. 1889-1893, March 1990).

Shuber teaches methods for obtaining genetic information from a biological sample comprising (a) providing a sample containing target nucleic acid molecules and (b) detecting the target molecules by contacting the sample with hybridization probes and identifying the hybridized probes (abstract). Shuber specifically teaches that the method can be used with 10-200 probes, preferably allele specific oligonucleotides (Col. 7, lines 11-14). Shuber teaches multiple embodiments for his invention.

With respect to claims 8 and 14, Shuber further teaches that hybridized probes can be identified by the use of hybridization arrays, wherein members of the probe pool are separated from the target nucleic acids and re-hybridized to immobilized probes on an array (Col. 9, line 65-Col. 10, line 10). In this case, the method of Shuber comprises obtaining genetic information from a sample by (a) providing probes that hybridized to target nucleic acid molecules in a sample and (b) detecting the probes using an ensemble of probes, wherein the detection ensemble is immobilized on an array, wherein the probes of step (a) were obtained by first hybridizing a probe pool (ensemble of ID probes) with the sample and then separating them from the sample.

Shuber further discloses in example 9 embodiment of the invention in which ligation based techniques are used (Col. 25, heading Example 9). In this case, probes that are intended to hybridize with the target are ligation probes and the ligation probes flank the site of a genetic alteration (Col. 26, lines 14-16). Shuber teaches that some probes which identify genetic

alteration include ASO probes, which target small changes relative to the prevalent "wild type" sequence, including a single nucleotide (as in single nucleotide polymorphisms (SNP)) (Col. 4, lines 40-48). Shuber teaches that after ligation the ligated products can be amplified using LCR or PCR (Col. 26, lines 31-34), specifically teaching that one method for identification of ligated probes is to use the ligation product as a template for a linear amplification using a universal priming sequence (Col. 26, lines 63-66).

Shuber does not specifically exemplify the universal priming sequences.

Straus *et al.* teach the use of adapters on the end of probes that allow amplification of a wide variety of sequences using a single primer pair (p. 1890). It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have used adapters such as those taught by Straus *et al.* in the methods taught by Shuber since Shuber suggests using a universal priming sequence and Straus teaches such a sequence. Furthermore, Straus *et al.* motivate the use of such primers when they point out that "Amplification of the remaining DNA, using the PCR provides enough DNA to proceed with the experiment. The PCR requires that template molecules be flanked by defined sequences that can hybridize oligonucleotide primers (p. 1891)."

14. Claims 7, 59, and 60 are rejected under 35 U.S.C. 103(a) as being unpatentable over Shuber in view of Bleiweiss et al. (J. of Reproductive Medicine, (Feb. 1992) 37(2) 151-156) or over Barany in view of Bleiweiss *et al.* or Greisen *et al.* in view of Bleiweiss *et al.*

Shuber teaches methods for obtaining genetic information from a biological sample comprising (a) providing a sample containing target nucleic acid molecules and (b) detecting the target molecules by contacting the sample with hybridization probes and identifying the hybridized probes (abstract). Shuber specifically teaches that the method can be used with 10-200 probes, preferably allele specific oligonucleotides (Col. 7, lines 11-14).

Barany et al. teach a method for identifying a plurality of sequences differing by one or more single base changes, insertions, deletions or translocations in a plurality of target nucleotide sequences (abstract). The method comprises (a) providing a sample containing target nucleic acid molecules (p. 6, lines 13-15) (b) detecting the target nucleic acid molecules by means of a hybridization phase in which two probes suitable for ligation when hybridized adjacent to one another on a target nucleic acid are hybridized to a target molecule and ligated (p. 6, lines 25-30) and (c) identifying the nucleic acid molecule by means of a capture phase in which the probes are captured on an addressable array (p. 6, lines 35-40) and identity is determined based on their position on the array (p. 7, lines 3-7). The method is exemplified in figure 8 wherein a single pair of amplification primers is used to amplify the region containing a mutation, and then a probe sets are used to detect different mutations in two different codons. In this example there are twenty possible mutation combinations.

Greisen *et al.* teach a method for detecting target nucleic acid molecules in a biological sample potentially comprising such target nucleic acid molecules, said method comprising the steps of:

(a) providing nucleic acid molecules that are (ii) probes that hybridize to the target nucleic acid molecules in said sample (p. 336); and

(b) detecting target nucleic acid molecules by contacting or comparing the nucleic acid molecules of (a) with a detection ensemble of nucleic acid sequences that has a minimum genomic derivation of greater than five and that comprises nucleic acid detection sequences that can detect the nucleic acid molecules of (a) (p. 338, Table 3).

Neither Shuber, Barany et al., nor Greisen *et al.* teach the use of their method with *in situ* hybridization.

Bleiweiss et al. teach a method in which they identify human papillomavirus subtypes using in situ hybridization probes specific to recognize subtypes 6/11, 16/18, or 31/35/51 (p. 151-152). In the methods of Bleiweiss *et al.* the biological sample is treated to make nucleic acids available for hybridization without purifying said nucleic acid molecules from the sample.

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have used an in situ hybridization as taught by Bleiweiss et al. in method of Shuber or in the method of Barany et al. because Bleiweiss teaches that in situ hybridization has the advantage of extreme sensitivity, and is preferable over Southern blot assays because of "its preservation of cellular and nuclear morphology, allowing precise localization of a positive signal (p. 154)."

15. Claims 16-18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Shuber in view of Barany et al.

Shuber teaches methods for obtaining genetic information from a biological sample comprising (a) providing a sample containing target nucleic acid molecules and (b) detecting the target molecules by contacting the sample with hybridization probes and identifying the hybridized probes (abstract). Shuber specifically teaches that the method can be used with 10-200 probes, preferably allele specific oligonucleotides (Col. 7, lines 11-14). Shuber teaches multiple embodiments for his invention.

In one embodiment, Shuber teaches that the nucleic acid to be identified comprise bacteria and their phages, viruses, fungi and protozoa (Col. 6, lines 5-9). Shuber teaches that the sample of nucleic acid can be isolated from a patient, particularly from any cell source or body fluid including blood cells, buccal cells, or tissue exudates at the site of infection (Col. 6, lines 13-23).

Shuber does not specifically identify any specific bacteria and their phages, viruses, fungi or protozoa that could be tested for in a nucleic acid sample.

Barany et al. teach a method for identifying a plurality of sequences differing by one or more single base changes, insertions, deletions or translocations in a plurality of target nucleotide sequences (abstract). Barany et al. teach that this method can be used to test for infectious diseases, including *Escherichia coli, Salmonella, Shigella, Pseudomonas, Mycobacterium tuberculosis, Mycobacterium avium-intracellulare, Yersinia, Staphylococcus aureus, Streptococcus pneumonia, Corynebacteria, Legionella, Mycoplasma, Chlamydia, Enterococcus faecalis, Cryptococcus neoformans, Blastomyces detmatitidis, Histoplasma capsulatum,*

Coccidioides immitis, Candida albicans, Entamoeba, and Necator americanis (p. 20, line 33- p. 21, line 23).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have tested for the nucleic acids of the specific pathogens taught by Barany et al. in the method taught by Shuber since Shuber teaches that his method can be used for the identification specific nucleic acid sequences of "part of a foreign genetic sequence, e.g. the genome of an invading microrganism" including bacteria and their phages, viruses, fungi and protozoa (Col. 6, line6-7), and Barany et al. specifically list these bacteria and their phages, viruses, fungi and protozoa as pathogens that could be detected in a nucleic acid assay.

16. Claims 53 and 54 are rejected under 35 U.S.C. 103(a) as being unpatentable over Shuber in view of Jarnik et al. or as being unpatentable over Barany et al. in view of Jarnik et al.

Shuber teaches methods for obtaining genetic information from a biological sample comprising (a) providing a sample containing target nucleic acid molecules and (b) detecting the target molecules by contacting the sample with hybridization probes and identifying the hybridized probes (abstract). Shuber specifically teaches that the method can be used with 10-200 probes, preferably allele specific oligonucleotides (Col. 7, lines 11-14). Shuber discloses in example 9 embodiment of the invention in which ligation based techniques are used (Col. 25, heading Example 9). In this case, probes that are intended to hybridize with the target are ligation probes and the ligation probes flank the site of a genetic alteration (Col. 26, lines 14-16). Shuber teaches that some probes which identify gentetic alteration include ASO probes, which

target small chages relative to the prevalent "wild type" sequence, including a single nucleotide (as in single nucleotide polymorphisms (SNP)) (Col. 4, lines 40-48). Shuber teaches that after ligation the ligated products can be amplified using LCR or PCR (Col. 26, lines 31-34), specifically teaching that one method for identification of ligated probes is to use the ligation product as a template for a linear amplification using a universal priming sequence (Col. 26, lines 63-66).

Barany et al. teach a method for identifying a plurality of sequences differing by one or more single base changes, insertions, deletions or translocations in a plurality of target nucleotide sequences (abstract). The method comprises (a) providing a sample containing target nucleic acid molecules (p. 6, lines 13-15) (b) detecting the target nucleic acid molecules by means of a hybridization phase in which two probes suitable for ligation when hybridized adjacent to one another on a target nucleic acid are hybridized to a target molecule and ligated (p. 6, lines 25-30) and (c) identifying the nucleic acid molecule by means of a capture phase in which the probes are captured on an addressable array (p. 6, lines 35-40) and identity is determined based on their position on the array (p. 7, lines 3-7). The method is exemplified in figure 8 wherein a single pair of amplification primers is used to amplify the region containing a mutation, and then a probe sets are used to detect different mutations in two different codons. In this example there are twenty possible mutation combinations.

Neither Shuber nor Barany teach the use of this method wherein amplification sequences are used to direct the amplification of sequences lying between Alu repeats using Alu-specific primers.

Jarnik et al. teach a method which comprises using inter-Alu PCR and using the PCR products as probes (p. 389, Col. 1) for the detection of genomic rearrangements and/or deletions in cancer cells.

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have used inter-Alu PCR and Alu probes in the method of Shuber or in the method of Barany et al. in order to have produced a method useful for detecting genomic rearrangements and/or deletions in cancer cells, or for other types of cancer detection methods since Jarnik et al. teach "In addition to the detection of LOH, inter-Alu PCR typing systems also detect genomic instabilities occurring in certain hereditary as well as in a fraction of sporadic cancer cells (p. 397)."

Response to Applicant's Remarks

The following remarks are reiterated from the previous action and address applicant's arguments provided in the response filed 8/17/00 (paper number 6).

Central to Applicant's arguments is the assertion that Shuber does not teach or obviate the two independent claims. Applicants arguments are not found persuasive for the reasons that follow.

Applicant argues that Shuber's primary focus is on the ability to scan numerous biological samples in parallel, while applicant's is on testing a single biological sample for the presence of distinct genomes or for numerous polymorphisms that occur throughout an entire genome. In response to applicant's argument that the references fail to show this feature, it is noted that this feature is not recited in the rejected claim(s). Although the claims are interpreted

in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). Furthermore, Shuber specifically teaches that his methods "have the capacity to cost effectively analyze a large number of samples (>500) for a large number of mutations (>100) in a single assay (Col. 5, lines25-28)," and further specifies that the methods can be used for the identification of multiple genes in a single patient's DNA sample, and that "the method is applicable when one or more genes or genetic loci are targets of interest (Col. 5, lines 54-57)." Thus, Shuber does in fact teach that his method can be used for the interrogation of unrelated sequences.

Applicant further argues that Shuber does not teach the use of a detection ensemble that has a minimum genomic derivation of 6 or more. However, in order to support this argument, applicant relies on a definition of "hybridizes to" found in the specification. This definition is not found in the claims, and is not considered to limit the claims since the term "hybridizes to" is a widely used term in the art and the broadest reasonable interpretation must be given to this phrase. The broadest interpretation would include the interpretation relied on in applicant's arguments, but would also include a more stringent hybridization conditions such as those used by Shuber. Shuber's intent is clearly to provide a set of probes which is able to distinguish between 32 different possible alleles in a sample (see table that bridges Col. 18 and 19), and as such, the example provided by Shuber is considered to have a minimum genomic derivation of greater than five as the base claim requires. With regard to claim 8, applicant argues that Shuber does not teach a step in which prior to step (a) nucleic acid molecules of the sample are hybridized with an ensemble of ID probes to yield the probes of step (a)(ii). Shuber does in fact

teach this limitation. Shuber teaches that two hybridization steps. First an ensemble is hybridized with the target nucleic acids (the sample). Then the members of the ensemble which hybridize with the sample are separated from the target nucleic acids, yielding the probes of step (a)(ii). Then, these probes are hybridized to the detection ensemble in order to determine the presence of the target nucleic acid in the sample. The method taught by Shuber does not differ from claim 8.

Applicant further argues that claim 8 requires hybridization to unpurified nucleic acids. This limitation is simply not found in claim 8.

Applicant argues that the disclosure of Barany *et al.* suffers from the same deficiencies as Shuber. The arguments presented with regard to Shuber are therefore applied with regard to Barany *et al.* as well. Barany *et al.* clearly intend that their invention be used for the simultaneous detection of a wide array of nucleotide sequences. This assertion is supported by the Barany *et al.*'s claims 51-54 wherein they specify method is used to detect infectious diseases caused by bacterial, viral, parasitic, and fungal infectious agents, and they further list over fifty examples of such agents.

Thus, the previous rejections are maintained. New rejections in view of Greisen *et al.* are also provided in this office action.

Conclusion

17. No claims are allowed.

18. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Juliet C. Einsmann whose telephone number is (703) 306-5824. The examiner can normally be reached on Monday through Thursday, 7:00 AM to 4:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W. Gary Jones can be reached on (703) 308-1152. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 and (703) 305-3014.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Juliet C. Einsmann
Examiner
Art Unit 1655

February 13, 2002

W. Gary Jones
Supervisory Patent Examiner
Technology Center 1600